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With his memory magnetically erased, a monkey knows he is uncertain

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Although intelligence is associated with what one knows, it is also important to recognize and to respond adaptively when one is uncertain. This competency has been examined developmentally and comparatively, but it is difficult to distinguish between objective versus subjective cues to which organisms may respond. In this study, transcranial magnetic stimulation was used to disrupt cognitive processing by a rhesus monkey (*Macaca mulatta*) in a computerized divided visual field memory task. When magnetic stimulation disrupted neural activity in the cerebral hemisphere that initially processed the visual images, recognition accuracy declined and use of the uncertain response significantly increased, relative to control conditions. Thus, the monkey tended to respond adaptively when he did not know the answer—where uncertainty was produced by targeted disruption of the neural processing of a stimulus—even in the absence of external, objective cues to corroborate his subjective, metacognitive assessment of uncertainty.

Keywords: uncertainty; metacognition; transcranial magnetic stimulation

1. INTRODUCTION

Intelligence is certainly related to the capacity to acquire and to use information, such that 'what one knows' is commonly assessed as an index of intelligence. However, it is also important for organisms to know when they *do not* know. That is, a hallmark of intelligence is the capacity to monitor when one is uncertain and to respond adaptively to this lack of knowledge. This metacognitive ability has a long research history in psychology (e.g. Nelson 1992), but has only recently been demonstrated convincingly in the studies of non-human animals (see reviews by Smith *et al.* 2003, 2008). One continuing challenge for the study of metacognitive judgements—particularly as these emerge developmentally or comparatively—has been to determine the degree to which judgements of uncertainly truly represent reflective, subjective, metacognitive events (i.e. the responder's own assessment of her/his uncertainty) rather than objective stimulus cues such as difficulty, infrequency or reward associations that tend to be correlated with or to produce uncertainty. The present study combines an established test paradigm with a relatively new neuroscientific technique to dissociate these potential response cues.

The divided visual field (DVF) paradigm has been used for years to explore functional cerebral asymmetries (Beaumont 1982), including with non-human primates (Hopkins *et al.* 1990). In the DVF paradigm, stimuli are flashed briefly (for less time than is required for a saccade) parafoveally to either side of visual fixation. Given the organization of primate vision, such an image is transmitted first to the contralateral cerebral hemisphere, and only subsequently and indirectly, via the corpus callosum, to the other hemisphere. Thus, an image that is flashed to the left of fixation is initially processed in the primary visual cortex of the right hemisphere (and vice versa), giving one hemisphere preferential access to the visual information with respect to time and quality. This paradigm has been used to study functional cerebral asymmetries in the processing of various types of stimuli (e.g. words, pictures). For the present investigation, we were interested in the opportunity the DVF paradigm allows selectively to disrupt cognitive processing so as to create response uncertainty.

We used the DVF paradigm in conjunction with transcranial magnetic stimulation (TMS; Walsh & Pascual-Leone 2005; Wassermann *et al.* 2008) of the left- or right-cerebral hemisphere. In the repetitive TMS procedure, an electromagnetic coil generates a rapid sequence of brief 2-T magnetic pulses. With the coil held against a head, the magnetic energy passes painlessly through skin and bone, but can stimulate neural firing in a region of cortex beneath the coil. The extent and duration of neural activation varies as a function of the intensity and sequence of stimulation. This neural firing can create a temporary, functional 'lesion'—an area where normal neural activity is safely disrupted, interfering with stimulus processing until the TMS ceases.

We hypothesized that post-stimulus TMS would disrupt the monkey's recognition memory for a stimulus that was briefly and unilaterally presented, and that this effect would be particularly pronounced when TMS was administered to the hemisphere contralateral to the visual field of stimulus presentation. That is, we expected TMS to create neural interference that would impair memory for a stimulus, particularly when the stimulus was transmitted first to the hemisphere that received the TMS. We were further interested in how TMS would affect the animal's use of a third response option, an 'I don't know' response that would remove any chance for the animal to make an error on that trial.

2. MATERIAL AND METHODS

We tested a 5 year old male rhesus monkey (*Macaca mulatta*) on a computerized DVF task (figure 1*a*) that assessed the animal's recognition memory for which stimulus had been flashed. The rhesus monkey was not reduced in body weight or deprived of food or fluid for purposes of testing. The animal was restrained in a Primate Products chair during test sessions, and completed every trial with his right hand. He initiated each trial via joystick movements, and thus controlled whether he worked or rested and, indirectly, whether or not he received TMS.

In the previous training, the macaque had learned to manipulate a joystick to respond to computer-generated stimuli in accordance

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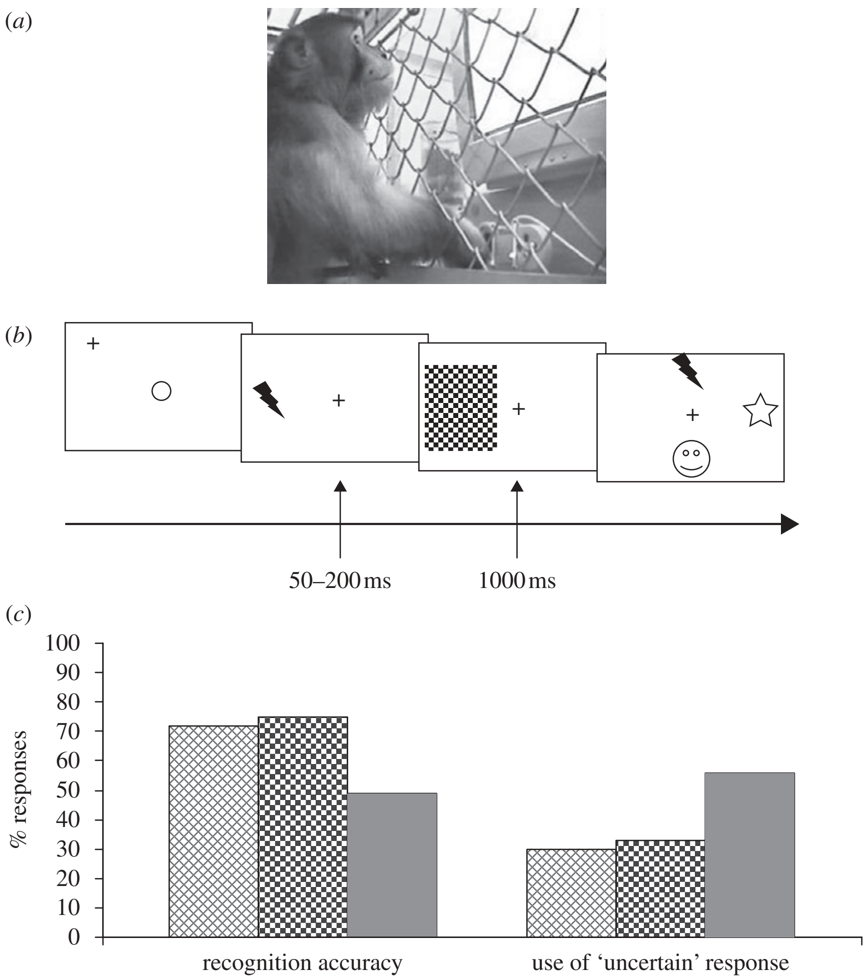

Figure 1. (*a*) A rhesus monkey manipulates a joystick in response to a computer-generated stimuli. (*b*) A schematic of the computerized DVF task used in this study. (*c*) Percentage of correct-recognition responses and percentage of responses to the uncertain response option, as a function of condition. Boxes with crosses, no TMS; boxes with squares, TMS to hemisphere opposite initial stimulus processing; shaded boxes, TMS to same hemisphere as initial stimulus processing.

with the demands of numerous tasks, including the DVF and uncertainty paradigms used in the present study. Similarly, the animal had experienced TMS while performing psychomotor tasks before the present study. However, the data analysed for this report are the first and only time the animal completed DVF with the opportunity to use the uncertainty response, and reflect all the animal's TMS trials on this task.

Figure 1*b* shows the design of the study. The monkey initiated each trial by manipulating a joystick so as to bring a computer-generated cursor into the centre of a midscreen circle. The difficulty of centering the cursor ensured that the animal fixated midscreen, whereupon a randomly selected visual image (like those described by Rumbaugh *et al.* 1989; Washburn & Rumbaugh 1992) was flashed 4° to the left or right side of fixation. Presentation duration was randomized between 50 and 200 ms each trial to ensure that performance remained below ceiling. Immediately after stimulus offset, a checkerboard pattern appeared in the stimulus location for 1 s to mask any visual/screen persistence. The monkey was then presented a choice between two images in a memory test. If the animal picked the image that had been flashed on that trial, he received a fruit-flavoured pellet. A brief timeout followed incorrect responses. All images and locations were randomly determined.

A final task manipulation is also displayed in figure 1*b*. During the recognition-test phase of the DVF task, the monkey could select a third response option (a star) to remove the incorrect image from the screen, such that the monkey could only subsequently choose the correct image on that trial. The monkey could use this 'uncertain' option on any trial, but as the use of this response slowed the trial's pace and the rate of reward procurement, the most efficient pattern would be to use this response only when the animal was uncertain which image had been flashed.

Before each experimental session, the TMS coil was used to stimulate various points on the monkey's head so as to locate the position of the motor strip, as evidenced by stimulation-induced finger twitches. The intensity of stimulation was then adjusted to find the lowest intensity that resulted in observable digit movements. TMS intensity during the DVF task was calibrated each session at 10 per cent above this motor threshold.

Prior to each trial, the magnetic coil was positioned against the monkey's head over either the left or right cerebral hemisphere, above the ear, immediately anterior to the motor cortex. This procedure provided no cue as to whether magnetic stimulation would be present on any particular trials, and the position of the magnet was uncorrelated with the position in which the visual stimuli appeared.

On some randomly selected trials, the monkey received 1 s of 10 Hz repetitive TMS to the cerebral hemisphere contralateral to the visual field of stimulus presentation (e.g. the stimulus flashed to the left of fixation, and TMS was presented to the right hemisphere—the same cerebral hemisphere that first received the visual stimulation). On other trials, TMS was presented to the hemisphere ipsilateral to the visual field of stimulus presentation (i.e. the hemisphere opposite initial stimulus processing). In all instances, TMS was administered during the interval when the checkerboard was onscreen (after stimulus presentation, before response), and the parameters of TMS (timing, duration, intensity, frequency) was the same for all trials in which it was used. The monkey received a small amount of fruit juice on every trial in which TMS was administered.

3. RESULTS

The results of this study confirm that the rhesus monkey did monitor and respond to its subjective uncertainty states. Figure 1*c* shows that accuracy on trials ($n = 140$ trials) in which TMS was administered to the cerebral hemisphere opposite of initial stimulus processing (e.g. stimuli flashed to the right-visual hemifield and thus transmitted initially to the left-cerebral hemisphere, with TMS to the right-cerebral hemisphere) was comparable to the performance on no-TMS trials ($n = 255$ trials; $z = 0.65$, $p > 0.10$). However, when TMS disrupted neural activity in the hemisphere of stimulus processing ($n = 163$ trials), performance dropped significantly ($z = 6.85$, $p < 0.001$) to chance level.

In this same TMS condition, the monkey was significantly ($z = 4.14$, $p < 0.001$) more likely to select the 'uncertain' response option. These effects did not vary by cerebral hemisphere of stimulation ($p > 0.10$).

4. DISCUSSION

No objective cue could indicate when the monkey should select the uncertain response in this test. A specific stimulus that the monkey recognized accurately on one trial could be erased from memory by TMS (and thus subject to uncertainty) on a subsequent trial. Moreover, the presentation of TMS itself could not cue the monkey to use the uncertain response. The noise and physical sensations that accompanied TMS were present on every stimulation trial; however, use of the uncertain response did not increase on all TMS trials, but only on trials in which TMS was administered to the hemisphere that was initially processing the stimulus for that trial. It seems unlikely that the animal learned in the few trials obtained here to associate the complex conditional events that would be required for an objective cue to use the uncertain response, and indeed use of the uncertain response was just as likely in the first 100 trials as in the overall data. Thus, the only available cue for when the animal should opt for the uncertain response was the animal's assessment of its own certainty about which image had been presented.

These data provide unique evidence that non-human primates monitor their own cognitive states. The findings also demonstrate that alert, behaving monkeys will, without coercion, perform cognitive tests while being stimulated with TMS—indicating promise for future non-invasive localization-of-cognitive-function studies. Note that the timing of the stimulation (after stimulus presentation, but before the animal was asked to make a manual response) minimizes the possibility that the present effects are perceptual or motor artefacts. TMS stimulation disrupted post-stimulus processing and retention of the to-be-remembered information, but did not prevent the monkey from seeing the image or from moving the joystick skilfully either to the stimulus the animal recognized or to the 'uncertain' response option. The fact that the monkey willingly initiated trials to receive TMS further suggests that follow-up studies are possible, for example to track the time-course of cognitive processing associated with recognition and metacognition by varying the interval between stimulus offset and magnetic stimulation.

The present results replicate studies in which monkeys have responded adaptively in memory tasks that require judgements about which the animals may be uncertain (Smith *et al.* 1998; Hampton 2001; Kornell *et al.* 2007), and extend those findings by eliminating cues that would link any particular stimulus or condition to the uncertain response. Although only one monkey was tested for this study, the highly reliable differences that were observed using this innovative procedure would seem to make this finding important for interpreting whether non-human primates can respond adaptively to subjective uncertainty cues.

The use of animals and procedures in this study were approved by the Georgia State University Institutional Animal Care and Use Committee.

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